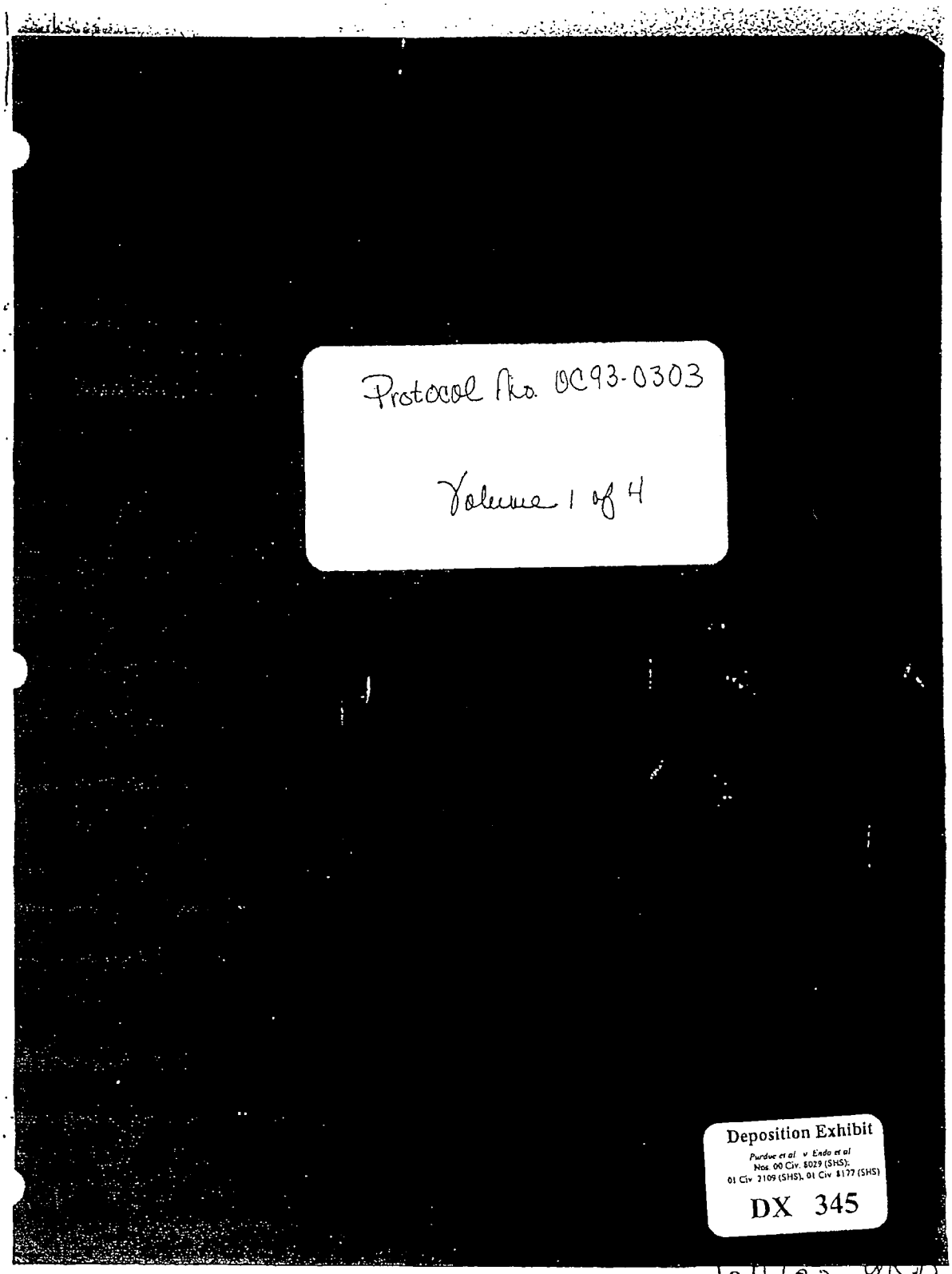

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STUDY REPORT

DOUBLE-BLIND, RANDOMIZED, REPEATED DOSE, CROSSOVER COMPARISON OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF CONTROLLED-RELEASE OXYCODONE AND CONTROLLED-RELEASE MORPHINE IN CANCER PATIENTS WITH PAIN

Sponsor

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Analytic Laboratory

Dr. Timo Seppälä
Department of Biochemistry
National Health Institute
Helsinki, Finland

Purdue Research Center
99-101 Saw Mill River Road
Yonkers, New York 10701
(914) 968-6000

Investigator

Eija Kalso, M.D., Ph.D.
Department of Anesthesia
Helsinki University Central Hospital
Haartmaninkatu 4 FIN-00290
Helsinki, Finland

STUDY DATES:

START DATE: February 22, 1994
END DATE: May 16, 1995

STUDY REPORT DATE: October 17, 1996

SIGNATURE SHEET

PREPARED BY

Susan Slagle, M.S.
Manager,
Biostatistics

Brian Burke, Ph.D.
Senior Manager,
Medical Writers

Rufus K. Marsh, Ph.D.
Senior Medical Writer,
Scientific Communications

REVIEWED BY

Robert F. Kaiko, Ph.D.
Vice President

Ronald Fitzmartin, Ph.D.
Executive Director, Biostatistics
and Clinical Data Management

APPROVED BY

Robert F. Kaiko, Ph.D.
Vice President
Date 10/25/96

Paul D. Goldenheim, M.D.
Vice President
Date 10/25/96

REVISIONS

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1		
2		
3		
4		

DOUBLE-BLIND, RANDOMIZED, REPEATED DOSE, CROSSOVER COMPARISON OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF CONTROLLED-RELEASE OXYCODONE AND CONTROLLED-RELEASE MORPHINE IN CANCER PATIENTS WITH PAIN

PROTOCOL NO. OC93-0303

SUMMARY

1. **TITLE/INVESTIGATOR/TRIAL DATES:** Double-Blind, Randomized, Repeated Dose, Crossover Comparison of the Pharmacokinetic and Pharmacodynamic Profiles of Controlled-Release Oxycodone and Controlled-Release Morphine in Cancer Patients With Pain/Eija Kalso, M.D., Ph.D. /The first patient was enrolled on February 22, 1994. The last patient finished the study on May 16, 1995.

2. **OBJECTIVES/STUDY DESIGN:** The objectives of this study were to estimate and compare the analgesic efficacy of the controlled-release (CR) formulations of oxycodone and morphine, to develop and compare pharmacokinetic/pharmacodynamic profiles for CR oxycodone and CR morphine after repeated oral q12h dosing, and to develop guidelines for the initiation of therapy with CR oxycodone.

This study was designed as a single-center, randomized, double-blind, multiple-dose, two-period crossover study with an initial randomized open-label titration period. Adult patients with stable, chronic cancer pain were chosen to enter the study. They were randomized to an open-label titration period, administered either CR oxycodone q12h or CR morphine q12h at 8 AM and 8 PM, and titrated to achieve pain control. Initial dosages were based on the patients' previous analgesic dosages; nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), were permitted if their use remained stable. Rescue medication, as either immediate-release (IR) oxycodone or IR morphine, was permitted, as needed. Titration was permitted for a maximum of 21 days and was defined as clinically successful when the patient's pain was, commonly, less than or equal to slight pain with two or fewer rescue doses per day for at least 48 hours without a change in the q12h dose.

Upon successful titration, patients were randomized to the two-period, double-blind crossover part of the study. Each double-blind period lasted for at least 4 days and up to 7 days with no washout between treatments. Pain intensity was rated four times a day, acceptability of therapy twice a day, and reports of nausea and emesis were elicited daily. On the last day of each double-blind period, phlebotomies were performed at 0, 1, 3 to 4, and 5 to 6 hours after the 8 AM dose.

Pharmacodynamic measurements were obtained for pain intensity and drug effects. Drug effects were rated by both the patient and an observer using the Modified Specific Drug Effect Questionnaire (MSDEQ).

There were no protocol amendments.

contributed to the larger number of rescue doses taken by patients treated with CR oxycodone.

Number of Dose Adjustments During Titration

Patients were titrated to stable pain with q12h doses of either CR oxycodone or CR morphine. The mean number of upward dose adjustments required to achieve stable pain control was not significantly different with CR oxycodone (2.6) or CR morphine (1.4). The majority of patients converted with fewer than three dose adjustments regardless of treatment: 10 (59%) patients with CR oxycodone and 15 (79%) with CR morphine.

Mean Daily Acceptability of Therapy During the Double-Blind Periods

For the intent-to-treat population the mean daily acceptability of therapy ratings for both periods combined was in the fair (3) to good (4) range. While the difference of approximately one quarter of a unit between CR oxycodone and CR morphine was statistically significant, it was not clinically meaningful and analysis of period 1 revealed no difference in acceptability of therapy ratings between treatments during period 1. These results are summarized below.

Mean Acceptability of Therapy During Last Three Days of Double Blind (Intent-to-Treat)

	CR Oxycodone			CR Morphine		
	Period 1	Period 2	Combined	Period 1	Period 2	Combined
3-Day Average	3.32	2.97	3.12*	3.31	3.55	3.41*

*Statistically significant treatment difference (p=0.0032)

NOTE: Additional analysis was conducted only for Period 1; no significant treatment differences were found.

Cross Reference: Table 11.1B

Safety

The adverse events in the study are summarized below. In both the titration phase and the double-blind periods, more than 95% of patients reported adverse events that were judged to be related to the study medications. The majority of drug-related adverse experiences with either treatment were mild or moderate severity: 92% with CR oxycodone and 91% with CR morphine. The difference between treatments in the incidence of adverse events was not significant. The most frequently reported adverse events were nausea, somnolence, constipation, dry mouth, vomiting, dizziness, pruritus, and sweating. All of these are commonly associated with opioid therapy. During the double-blind period the number of reports was greater with CR morphine.

3.0 FULL STUDY REPORT

3.1 Introduction

With their longer periods of pain control and their convenient dosages, controlled-release (CR) opioids have therapeutic advantages over immediate-release (IR) opioids. However, until recently the only oral CR opioid available was a q12h morphine formulation. Although this formulation has helped many patients, other CR opioids can provide therapeutic benefits for additional patients. A new CR tablet formulation of oxycodone (OxyContin™) has been developed by Purdue Pharma L.P., which has expertise in the development of CR oral dosage forms, especially in the area of analgesics.

Oxycodone hydrochloride is a well-known opioid analgesic; it has pharmacologic activity similar to that of morphine, the prototype of opioid analgesics. The oral potency of oxycodone compared to morphine is approximately one mg of oral oxycodone to two mg of oral morphine. However, in the present study a 1 to 1.5 dose conversion ratio was employed, rather than the more accurate 1 to 2 ratio[1-3], because CR oxycodone and CR morphine were available only in 20 mg and 30 mg tablets, respectively. Among opioids indicated for moderate to severe pain, oxycodone possesses a unique combination of characteristics: high oral bioavailability and a short elimination half-life. These characteristics may give oxycodone an advantage as a more efficiently titratable strong opioid. In the United States, oxycodone has long been available with either acetaminophen or aspirin in combination tablets. Until recently, oxycodone has been available only as a single entity as IR solutions or tablets. Purdue Pharma L.P. has developed OxyContin™ oral tablets in a range of dosage strengths to be administered every 12 hours rather than every 4 to 6 hours as with the other oxycodone products.

This study compared the safety and efficacy of the new CR oxycodone formulation q12h with the well-established CR morphine formulation q12h for the control of pain in cancer patients.

3.2 Study Objectives

The objectives of this study were:

A. To estimate and compare the analgesic efficacy of the CR formulation of oxycodone and that of morphine.

B. To develop and compare the pharmacokinetic and pharmacodynamic profiles for CR oxycodone and CR morphine after oral q12h dosing.

C. To develop guidelines for the initiation of therapy with CR oxycodone.

3.3 Investigational Plan

3.3.1 Overall Design and Plan of the Study

This was a single-site, randomized, double-blind, multiple-dose, two-period crossover study with an initial randomized, open-label titration phase, in which cancer patients with pain were randomly assigned to receive either CR oxycodone or CR morphine on a q12h schedule to achieve pain control.

Standard equianalgesic conversion ratios were used to determine initial dosages based on the patients' previous analgesic use. Patients' dose levels could be titrated for up to 21 days with rescue medication used, as needed. The amount of rescue medication taken was added to the CR dose to determine dose adjustments. Patients were titrated until stable pain control was achieved. This was determined by the patients and the investigator to be usually no more than slight pain for a period of at least 48 hours with two or fewer rescue doses per day.

Once patients' doses to achieve stable pain were determined, patients then entered double-blind treatment, which had a standard, randomized crossover design using a double-dummy technique for blinding drug administration. For the double-blind phase of the study, patients were randomly assigned to a treatment sequence of either CR oxycodone to CR morphine or CR morphine to CR oxycodone. The starting dose for the double-blind phase was based on the dose established with titration during the open-label phase. After completion of Period 1, patients immediately entered Period 2 and received the alternate treatment. Rescue medication was available as needed throughout double-blind treatment at a fixed dose based on the CR dose.

Double-blind treatment, designed to evaluate the pharmacokinetics and pharmacodynamics of the two study medications, consisted of two periods that together could last up to 14 days. Phlebotomies were taken for pharmacokinetic measurements on the last day of each of the double-blind periods between the fourth and the seventh day of dosing at 0, 1, 3 to 4, and 5 to 6 hours after the 8 am dose. Pharmacodynamic measurements consisted of pain intensity and drug effect ratings, as discussed in Section 3.3.7.2.2.

There were no amendments to the protocol.

3.3.2 Study Rationale/Discussion of Choice of Design and Control Groups

Patients recruited for this study were adult patients with chronic cancer pain. Such patients were selected because they required around-the-clock analgesia, their pain could usually be stabilized so that assessments could be made in a crossover study, and they were part of the intended population which could benefit from CR oxycodone.

The study was primarily designed to examine the pharmacokinetic and pharmacodynamic relationships between CR oxycodone and CR morphine. CR morphine tablets are a marketed product and are, therefore, an appropriate positive control agent. The study was also intended to develop guidelines for the initiation of titration and therapy with CR oxycodone tablets.

3.3.3 Study Population

To obtain the 34 patients who completed this study, adult patients with chronic cancer pain were considered for enrollment, based on the inclusion and exclusion criteria presented below. All inclusion criteria had to be present and all exclusion criteria had to be met for patients to be enrolled.

Inclusion Criteria Both male and female patients over 18 years of age with clinical evidence of chronic (longer than two months) cancer pain thought to require therapy with an opioid analgesic could be included. Coexisting disease (and associated therapy), if present, had to be stable for at least one week before entry and had to be expected to remain stable throughout the study. Among patients currently receiving only non-opioid analgesics, only those patients with greater than slight pain at the time of evaluation and over the past day were permitted to enter the study. Patients currently receiving opioid analgesics could enter the study regardless of their pain intensity ratings. All non-opioid medications with analgesic properties had to be dosed according to a stable regimen (not prn) prior to entry into the study and during the double-blind periods. Patients had to be willing and able to participate in all aspects of this investigational study, including taking oral medications, undergoing phlebotomies, and completing subjective evaluations. If they were out-patients, they had to be able to be contacted by telephone. Patients had to be able to read, understand, and sign the written informed consent statement.

Exclusion Criteria Patients were excluded if they were allergic to oxycodone or morphine, but patients who had experienced common opioid side effects were not excluded. Patients were excluded if they had contraindications to opioid therapy, such as paralytic ileus or severe pulmonary disease (see Appendices II and III of the protocol). All opioids had to be stopped prior to entry into the study, and patients could not be receiving a non-study opioid medication that could not be discontinued. Patients were excluded who had a current or past history of severe organ dysfunction of the lungs, gastrointestinal tract, kidneys, liver or the central nervous system, a physical or psychological disease, or a laboratory diagnosis that, in the judgment of the investigator, might affect the patients' safety or that might confound the interpretation of this investigation. Patients were excluded if they were enrolled in other investigational clinical studies or were pregnant or nursing. Patients who could not take oral medications were excluded, as were patients who expected to have surgery or other procedures that would prevent their completion of the study.

3.3.4 Treatment Allocation/Randomization

Patients were randomized to receive either CR oxycodone or CR morphine when they entered the open-label titration at the beginning of the study. If titration was successful, patients entered the double-blind part of the study and were randomized to a treatment sequence of either CR oxycodone to CR morphine or CR morphine to CR oxycodone. Forty-five patients enrolled in this study; for titration, 23 were randomized to receive CR oxycodone and 22 to receive CR morphine. Thirty-six were randomized to double-blind treatment sequences, and 34 patients completed both double-blind periods.

Some of the patients enrolled early in the study were not assigned to treatment in a sequential fashion, as planned, because of a misunderstanding about the implementation of the randomization schedule. These patients were assigned to a treatment sequence but not the one specified in the randomization schedule. As a result, in the first period more patients (20 compared to 16) were treated with CR morphine and in the second period, more (20 compared to 14) were treated with CR oxycodone.

3.3.5 Study Drugs

The determination of initial CR oxycodone and CR morphine dosages in the open-label titration phase was based upon the opioid doses that patients had been taking recently and utilized conversion factors derived from well-controlled studies of relative analgesic potency. The availability of CR oral oxycodone in 20 mg tablets and CR oral morphine in 30 mg tablets required the calculated dose to be rounded to the nearest appropriate multiple of these dosages. For double-blind treatment, the dosages were the amounts of controlled-release opioid established during titration and also reflected the constraints imposed by the tablet strengths for CR oxycodone and CR morphine tablets.

Study medication tablets were supplied in bulk by The Purdue Frederick Company, for Purdue Pharma L.P., and rescue analgesic in liquid form was supplied by the study site.

3.3.5.1 Test Materials

Test Treatment

Drug Name: Oxycodone hydrochloride, controlled-release
Dosage Form: Tablets
Strength: 20 mg
Lot Numbers: Y8
Expiration Dates: Ongoing stability during study

Matching placebo tablets for CR oxycodone: 20 mg placebo

Reference Treatment

Drug name: Morphine Sulfate, controlled-release
Dosage Form: Tablets
Strength: 30 mg
Lot Numbers: CB 24-06
Expiration Dates: Ongoing stability during study

Matching placebo tablets for CR morphine: 30 mg placebo tablets

Rescue Analgesic Medication

For Test Treatment: Immediate-release oxycodone solution, 2.7 mg/mL

For Reference Treatment: Immediate-release morphine solution, 4.0 mg/mL.

3.3.5.2 Dosage/Administration/Route/Exposure

Open-Label Titration

Each patient who qualified for enrollment was assigned a unique open-label, patient randomization number in sequential ascending order. Patients were randomly assigned by patient number to receive either CR morphine 30 mg tablets, or CR oxycodone 20 mg tablets, each administered orally q12h around-the-clock at an initial dose based on prior opioid use using standard techniques and conversion charts (Appendix IV of protocol). This initial calculated dose (mg) was then rounded to the nearest multiple of the tablet strength for the assigned drug treatment. Patients took the appropriate number of tablets to achieve the initial total rounded q12h dose (mg). The initial dose was then titrated upward or downward to achieve stable pain control with acceptable side effects. The protocol did not have a maximum allowable upper dose limit; the lowest dose was based on the tablet strengths of either 20 mg q12h oxycodone or 30 mg q12h of morphine. Patients could be treated in this open-label period for up to 21 days.

The use of liquid rescue medication was determined as explained below.

Patients were told to return all unused medication and any empty bottles supplied for titration to the investigator after participation in the open-label period was completed.

Double-Blind Periods

The total daily oral oxycodone or morphine requirement during the double-blind periods was based on the results of titration. Each patient who achieved stable pain control was randomly assigned to a treatment sequence (oxycodone→morphine or morphine→oxycodone) in the double-blind period.

The double-blind randomization numbers were listed separately from the open-label randomization series; double-blind numbers were to be assigned in sequential ascending order. Dosing in each period was for 4 to 7 days. The patients then received two bottles of medication, one containing active tablets of either CR oxycodone or CR morphine, as determined by the patient's double-blind randomization number, and the other bottle containing placebo tablets of the alternate treatment.

Rescue Medications

Rescue medication was available in liquid form for oral administration; the volume of each dose was based on each patient's opioid requirement. The concentrations of the solutions were 4.0 mg/mL for morphine and 2.7 mg/mL for oxycodone; this permitted the volume (mL) of each rescue dose for an individual patient to be the same during both double-blind periods. Both liquid rescue medications tasted and looked the same. The rescue medication solution dispensed was the same opioid as the active q12h drug treatment. Rescue medication was administered as needed for pain between q12h doses and could be taken up to every 4 hours at approximately 1/3 to 1/4 the q12h dose of CR oxycodone or CR morphine. For patients with incident pain, rescue medication was given one hour before the activity likely to cause pain. During titration the q12h doses were increased to include the amount of rescue analgesic if more than two doses were taken per day. The rescue dose was adjusted according to any upward or downward titration of the q12h dose in order to maintain the rescue dose at 1/3 to 1/4 of the q12h dose. During the double-blind periods, the q12h doses remained stable regardless of the number of rescue doses taken.

3.3.5.3 Blinding/Packaging

The sponsor shipped study medication to the study site packaged in bulk bags for CR morphine, CR placebo morphine, and CR placebo oxycodone and packaged in bulk bottles for CR oxycodone. Medication was individually packaged on a per patient basis by the hospital pharmacy at the site, using randomization codes developed by Purdue Pharma L.P. Department of Biostatistics and Clinical Data Management.

Study analgesic consisted of a scheduled analgesic medication taken every 12 hours (q12h) and rescue analgesic medication taken as needed (prn). The q12h analgesic was administered openly in the initial titration period and was blinded using a "double-dummy" technique for Periods 1 and 2 of the double-blind treatment. Using this blinding technique, patients took an equal number of active and placebo tablets.

For double-blind treatment, the tablets of CR oxycodone and CR morphine were packaged separately for each of the two sequential periods: Period 1 and Period 2. The pharmacists packaging the tablets were not blinded to the treatment, but the investigator, other study staff, patients, and clinical monitors were blinded. The medications were packaged for a double-blind study, using a double-dummy technique. The dose administered was based on the dose which achieved stable pain control in the open-label phase. Patients received one bottle of active tablets as per the treatment randomization assignment, and one bottle of placebo tablets for the alternate treatment. For each q12h dose patients were to take an equal number of both the active and placebo tablets. The q12h oral dose (number of

tablets) was to remain the same during both double-blind periods, except that in Period 2, the active and placebo tablets were the reverse of those dispensed in Period 1.

The quantity of tablets dispensed was dependent on the dose to be administered. For every milligram of oral CR oxycodone administered q12h during the double-blind periods, 1.5 milligrams of oral CR morphine was administered q12h. The 1 to 1.5 ratio was employed, rather than the more accurate 1 to 2 ratio[1,3], because CR oxycodone and CR morphine were available only in 20 mg and 30 mg tablets, respectively.

Liquid rescue medications were blinded to both taste and appearance. Both solutions were prepared by dissolving the oxycodone or morphine in a solution of water and aqua mentrae piperitae cum conservens, which accomplished the blinding.

Before the study was unblinded, a member of the sponsor's Clinical Supplies Department reviewed a copy of the drug accountability records to verify that the medication dispensed was the same as the double-blind treatment assigned to the randomization number.

3.3.5.4 Breaking Double-Blind Codes

The treatment blind was maintained throughout the double-blind periods. The treatment assignment was unmasked on August 21, 1995 at 2:45 PM, following establishment of patient evaluability on August 18, 1995 with a database lock on August 21, 1995 at 2:00 PM.

3.3.5.5 Unused Medications

An accurate and timely record of the disposition of all clinical supplies was maintained on the inventory forms (Drug Accountability Forms) provided by the sponsor or on comparable forms. The supplies and inventory records were available upon request for inspection by the designated representative of the sponsor; however, the clinical monitor did not review the records until after the study was unblinded.

Unused study medication which had been dispensed was to be returned, along with empty containers by each patient to the investigator. The balance of (1) undispensed tablets of CR morphine, CR morphine matching placebos, CR oxycodone in opened bottles, and CR oxycodone matching placebos and (2) tablets returned by patients were destroyed at the site in accordance with local regulations at the study's conclusion after the reconciliation of the drug supplies with the sponsor. The active CR oxycodone 20 mg tablets which had not been dispensed and which were in unopened, sealed bottles (as shipped from sponsor) were transferred for use in protocol OC94-0505. Study OC94-0505 would be conducted by Dr. Kalso, the same investigator who conducted this trial, at the same institution. A total of 9 bottles of 500 tablets/bottle (4,500 tablets total) were transferred.

Patients Receiving Single Entity "Strong" Opioid Analgesics

If patients had been receiving single-entity strong opioids, the total daily oral oxycodone or morphine equivalent dose was calculated based upon their past three days of analgesia therapy, using standard conversion charts (Appendix IV of the protocol) derived from well-controlled relative potency analgesic studies. A conversion ratio of oxycodone to morphine of 1:2 was used to determine the initial dose in the open-label titration phase. The available strengths of CR oral oxycodone (20 mg) and CR oral morphine (30 mg) required rounding off doses to the nearest appropriate multiple of 20 mg (for patients randomized to oxycodone) or 30 mg (for patients randomized to morphine). For either CR oxycodone or CR morphine, the total daily dose was halved, rounded to the closest available dosage and administered at q12h ± 1 h. Both CR regimens were dosed on an "around-the-clock", not on an "as needed" basis.

Open-Label Titration

Study Medication Dosing

The goal of titration was an acceptable level of pain relief (most commonly none to slight pain with ≤ 2 rescue doses per day) without unacceptable adverse events while maintaining a stable total daily opioid dose for at least 48 hours. Patients were randomized to receive either CR oxycodone or CR morphine in an open-label fashion to provide for the titration of q12h dosages. During this time, patients took either IR morphine or IR oxycodone (same as q12h treatment) as rescue medication for breakthrough or incident pain. If necessary, patients had non-opioid co-analgesics introduced and their dosages stabilized. The protocol permitted patients 21 days to achieve stable dosing; if utilizing these titration procedures did not achieve stable dosing, the patients were discontinued from the study.

Rescue Analgesic Medication

See Section 3.3.5.2

Titration Guidelines

Upward or downward dose titration continued until the optimal dose, balancing the patient's pain level and adverse events, was established for at least 48 hours. If pain was at the moderate or severe level or if more than two rescue doses were used for breakthrough pain in a 24-hour period, the q12h total daily oxycodone or morphine dose was increased. The amount given as rescue medication in the preceding 24 hour period was used to recalculate the q12h dose. If the around-the-clock dosing was not increased in these circumstances, a written explanation was given on the case report form. All evaluations noted in the "Evaluations during Titration" section were followed during the titration.

Downward Titration

Downward titration was used if opioid adverse events were unacceptable, i.e., not manageable with appropriate treatment. When dose reduction was required, patients' q12h dose of study medication was decreased by at least 1/4 the number of tablets, depending on the severity of the adverse effects. Dose reduction continued until the adverse events disappeared or were, along with pain intensity scores, "acceptable" to the patient and physician.

Use of Coanalgesics

If, with the utilization of these titration procedures and with the appropriate treatment of adverse events, an optimal dose of q12h study medication could not be established, then non-opiate coanalgesics, e.g., tricyclic antidepressants or NSAIDs could be initiated or titrated as indicated while keeping the q12h study analgesic stable at an appropriate dose. After patients were stabilized with the use of adjuvant coanalgesics, they could be randomized to double-blind treatment and continue the same dose of coanalgesics.

Procedures during Double-Blind Treatment

Medication for Period 1 of the double-blind treatment was determined by the patients' randomized, double-blind, crossover sequence. The q12h dose of CR oxycodone or CR morphine was determined from the final dose in open-label titration. If the drug for the first period was not the same as the titration drug, the amount was calculated by the pharmacists using a ratio of oxycodone to morphine 1:1.5. The pharmacist packaged the medication accordingly, using a double-dummy technique.

When the goal of titration (most commonly none to slight pain and ≤ 2 rescue doses per day without unacceptable adverse events and with a stable total daily opioid dose for at least 48 hours) was achieved, the patients returned for a visit, before the last morning dose of the titration medication. At this time, vital signs were again measured and recorded. The last dose of titration medication was taken that morning during this visit, and then all titration drug and containers were collected.

The first dose of double-blind medication was taken in the evening (this day was designated Day 0). Patients were instructed to take their medication in the morning and 12 hours later $\pm$ 1 hour in the evening for 3 to 7 days. All evaluations noted above were followed during both double-blind periods; blinded rescue medication could be taken at any time, but not more frequently than every 4 hours.

Pain Intensity Ratings at Blood Sampling Times

Pain intensity ratings on both the CAT scale and VAS are shown in Tables 12.2A and 12.2B for the safety and efficacy and intent-to-treat populations, respectively, for each timepoint on phlebotomy days. The pain intensity ratings at each timepoint on the phlebotomy days in the intent-to-treat population for all periods combined are summarized below.

Mean Pain Intensity Ratings at Time of Phlebotomy

	CR Oxycodone (N=34)				CR Morphine (N=34)			
	0 Hour	1 Hour	3-4 Hours	5-6 Hours	0 Hour	1 Hour	3-4 Hours	5-6 Hours
VAS								
Mean	29.7	20.6	17.8	14.9	21.6	16.1	17.9	14.8
SE	4.2	3.2	3.4	2.6	3.4	3.4	3.5	3.2
CAT								
Mean	1.32	0.97	0.79	0.85	1.03	0.76	0.82	0.74
SE	0.15	0.12	0.13	0.10	0.13	0.13	0.12	0.11

Cross Reference: Table 12.2B

There were no significant differences in mean pain intensity by timepoint between treatments. Pain was well-controlled on both treatments and decreased after dosing.

Time to Achieve Stable Dosing

The time to achieve stable dosing was defined as the total number of titration days required to attain a stable dose which produced good daily pain control (mean pain intensity ≤ 1.25 on CAT scale) and required minimal rescue medication (≤ 2 doses/day). The percentage of patients successfully titrated to stable pain as defined for analysis and the number of days required to attain a stable dose with CR oxycodone and CR morphine are shown below.

Patients Titrated to a Stable Dose

	CR Oxycodone (n = 23)[a]		CR Morphine (n = 22)		Total (n = 45)	
	n	(%)	n	%	n	%
Titration						
Successful	16	(70)	18	(82)	34	(76)
Unsuccessful	7	(30)	4	(18)	11	(24)
Days to Stable Pain						
0	8	(35)	9	(41)	17	(38)
1-2	3	(13)	6	(27)	9	(20)
3-4	2	(9)	1	(5)	3	(7)
> 4	3	(13)	2	(9)	5	(11)
Median[b]	3		1.5			

[a] A higher number of patients treated with CR oxycodone (8) than CR morphine (4) received an incorrect titration dose.
[b] Median derived using product limit estimation.

Cross Reference: Table 6

Seventy percent of patients treated with CR oxycodone and 82% of those treated with CR morphine were titrated to stable pain. Thirty-eight percent of patients converted directly without need for titration or dose adjustment; 85% of those successfully titrated reached a stable dose by the fourth day of dosing. The median time to stable dosing was 3 days for CR oxycodone and 1.5 days for CR morphine. There were no significant differences in the time to achieve stable pain control. The time to stable dosing was 0 days for the largest percentage of patients in either treatment group.

It should be noted that most patients who were successfully titrated and entered the double-blind period (25 of 36) had previous regimens that included morphine whereas only 8 patients had previous regimens that included oxycodone, and this may have favored morphine over oxycodone in the time needed to achieve stable dosing. Nevertheless, there were no statistically significant differences in time to stable dosing between treatments.

Secondary Efficacy Variables

Mean Number of Rescue Doses during Double-Blind Periods

The mean number of rescue doses taken during the last 3 days of the double-blind periods of the study and the average over the last 3 days are shown for the intent-to-treat population (Table 8.1B) and for the safety and efficacy population (Table 8.1A). Overall for the intent-to-treat population the average number of rescue doses ranged from 0.8 to 1.5 per day. The average number of rescue doses never exceeded two per day on any day in either period and this was within the limits of the definition of stable pain established during titration.

For both double-blind periods combined, the mean number of rescue doses taken by the patients in the intent-to-treat population was significantly higher with CR oxycodone compared with CR morphine for the 3-day average. Analysis of Period 1 showed no significant differences between treatments in the mean number of rescue doses taken on any day. In the safety and efficacy population, similar results were observed. The results for the intent-to-treat population in the double-blind periods are summarized below.

Mean Rescue Doses in the Intent to Treat Population During the Last Three Days of Double-Blind Periods

	Period 1		Period 2		Combined	
	CR Oxy	CR Morph	CR Oxy	CR Morph	CR Oxy	CR Morph
3-Day Average	1.21	0.80	1.60	0.93	1.43*	0.85*

* Significant treatment differences: 3-day average (p=0.0038).
NOTE: Additional analysis was conducted only for Period 1; no treatment differences were found.
Cross-reference: Table 8.1B

The relatively short duration of action reported for IR oxycodone[1,2] compared to IR morphine may have contributed to the larger number of rescue doses taken by patients during treatment with CR oxycodone. Analysis of rescue use during period 1 showed no significant difference between treatments.

Number of Dose Adjustments during Titration

Patients were titrated to stable pain with daily doses of either CR oxycodone or CR morphine. The goal of titration was an acceptable level of pain relief without unacceptable adverse events and, most commonly, a pain intensity score of none or slight on the CAT scale with no more than two rescue doses a day and the maintenance of a stable total daily dose for at least 48 hours. The number of upward dose adjustments required to achieve stable pain control with CR oxycodone and CR morphine is shown below for the intent-to-treat population. The majority of patients in each treatment group converted with fewer than three dose adjustments: 10 (59%) patients who received CR oxycodone and 15 (79%) patients who received CR morphine. Also shown is the number of patients successfully titrated and the mean and median number of dose adjustments required in each group. Given that most patients had received morpine before entering the study, it is not surprising that there was a trend toward fewer upward dose adjustment with morphine, compared to oxycodone. Nevertheless, there were no significant differences between treatment groups.

Number of Upward Dose Adjustments during Titration (Intent-to-Treat)

	CR Oxycodone		CR Morphine		Total	
	n	(%)	n	(%)	n	(%)
None	7	(41)	7	(37)	14	(39)
1	1	(6)	3	(16)	4	(11)
2	2	(12)	5	(26)	7	(19)
≥ 3	7	(41)	4	(21)	11	(31)
n	17		19		36	
Mean	2.6		1.4		2.0	
Median	2.0		1.0		1.5	

Cross Reference: Table 5

The doses administered during titration are summarized in Table 5A and 5B, including the initial, final, and mean doses. Also shown is the number of patients converted from their prior analgesic to the closest possible dose of their titration medication and from their prior analgesic to a dose that was not the closest possible dose. There were 12 patients who were not converted to the closest possible dose using the recommended conversion factors for this study. Three of them (25%) subsequently discontinued for adverse experiences: 2 on CR oxycodone and 1 on CR morphine.

Mean Daily Acceptability of Therapy During the Double-Blind Periods

Tables 11.1A and 11.1B show CAT scores for the mean daily acceptability of therapy of patients during the last three days of each double-blind period and for both periods combined.

For the intent-to-treat population (Table 11.1B) and the safety and efficacy population (Table 11.1A), the mean daily acceptability of therapy ratings on Days 1 and 2, and averaged over 3 days were higher for patients treated with CR morphine compared to CR oxycodone. However, the differences were small and not clinically meaningful; both

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TABLE 5A

SUMMARY OF OPEN LABEL TITRATION

Population: All Patients Enrolled in Study

	CR Oxycodone		CR Morphine		Total	
	N	%	N	%	N	%
Entered Titration	23	(100.0)	22	(100.0)	45	(100.0)
No. Entered Double-Blind	17	(73.9)	19	(86.4)	36	(80.0)
Initial Total Daily Dose @ (CR Oxycodone / CR Morphine)						
40 / 60	8	(34.8)	8	(36.4)	16	(35.6)
80 / 120	7	(30.4)	4	(18.2)	11	(24.4)
120 / 180	4	(17.4)	4	(18.2)	8	(17.8)
160 / 240	1	(4.3)	1	(4.5)	2	(4.4)
200 / 300	1	(4.3)	2	(9.1)	3	(6.7)
> 200 / > 300	2	(8.7)	3	(13.6)	5	(11.1)
N	23		22			
Mean	100.9 *		182.7 *			
Std. Error	15.9		33.1			
Min	40		60			
Max	320		660			
Final Total Daily Dose @ (CR Oxycodone / CR Morphine)						
40 / 60	4	(17.4)	5	(22.7)	9	(20.0)
80 / 120	5	(21.7)	6	(27.3)	11	(24.4)
120 / 180	4	(17.4)	3	(13.6)	7	(15.6)
160 / 240	1	(4.3)	3	(13.6)	4	(8.9)
200 / 300	3	(13.0)	0	(0.0)	3	(6.7)
> 200 / > 300	6	(26.1)	5	(22.7)	11	(24.4)
N	23		22			
Mean	167.0		231.8			
Std. Error	25.6 #		46.4 #			
Min	40		60			
Max	480		840			

(Continued)

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CROSS REFERENCES:
Data Listing: 1, 9.2A, 9.2B, 12.1A, 12.1B and 12.1C
Statistics: Appendix IV

* Statistically significant difference between variances (p=0.0015) and means (adjusted for unequal variances: p=0.0335).

\# Statistically significant difference between variances (p=0.0101).

@ No statistically significant differences in distribution of doses.

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